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New Drug Mechanisms

Bedaquiline

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In this series we draw attention to medicines that have entered the European market with an entirely new mechanism of action. Publication is not to be confused with endorsement of use in clinical practice. Copyright of the images belongs to Leiden University, but use of the images (also available at http://coo.lumc.nl/trc and in the app stores) is free.

Introduction

Tuberculosis (TB) is typically caused by *Mycobacterium tuberculosis*, a pathogen which usually infects the lungs [1]. The incidence of strains that are resistant to first line TB treatment has increased in the last two decades. Consequently, there is a high medical need for novel new tuberculosis drugs [2].

Mechanism

Bedaquiline is the first drug on the market to target the mycobacterial ATP synthase. The production of ATP by the enzyme ATP synthase is crucial for cell survival of both prokaryotic and eukaryotic cells [2]. ATP synthase consists of a transmembrane (F_0) and a cytoplasmic (F_1) domain [3]. Proton flow through the F_0 domain leads to a rotation of the c and γ subunits of the F_1 domain. This rotation drives ATP synthesis at the $\alpha_3\beta_3$ hexamer (Figure 1, [4]). The main binding site of bedaquiline is located between the a and c subunits of the F_0 domain, near amino acid residue Glu61 [3–5]. Upon binding, bedaquiline inhibits ATP synthesis by blocking the proton flow and the subsequent conformational changes. This causes cell death in both replicating and non-replicating mycobacteria, making bedaquiline a bactericidal antibiotic (Figure 2, [6]). Bedaquiline is selective towards mycobacterial ATP synthase, compared with the human homologue, despite high similarity in protein sequence [7].

Indication

Bedaquiline has been granted market authorization for the treatment of tuberculosis [1]. The current indication covers its use as part of a combination regimen to treat pulmonary multidrug-resistant tuberculosis (MDR-TB) [6].

Clinical application

In a phase IIb trial in MDR-TB patients, the addition of bedaquiline to a background regimen significantly reduced the time to sputum conversion [8]. However, there were more deaths in patients treated with bedaquiline compared with placebo, and an explanation for this has yet to be found [8]. Because of this, bedaquiline should only be prescribed when alternative treatment options are unavailable [9, 10]. The dosing regimen consists of 400 mg orally once daily for 2 weeks, followed by 200 mg orally three times weekly with a total treatment duration of 24 weeks [9]. Bedaquiline is metabolized by CYP3A4 and so co-administration with CYP3A4-inducers/inhibitors should be avoided. The use of directly observed therapy has been recommended to promote therapeutic compliance.

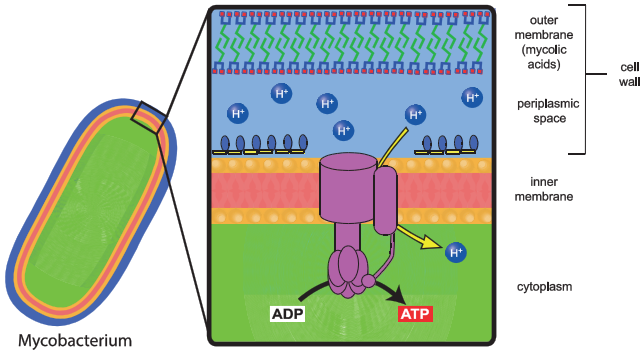

Figure 1

Production of ATP by mycobacterial ATP synthase. ATP synthase facilitates proton flow from the periplasmic space to the cytoplasm. The proton flow drives conformational changes that catalyze the production of ATP from ADP and inorganic phosphate. This process is crucial to cell survival

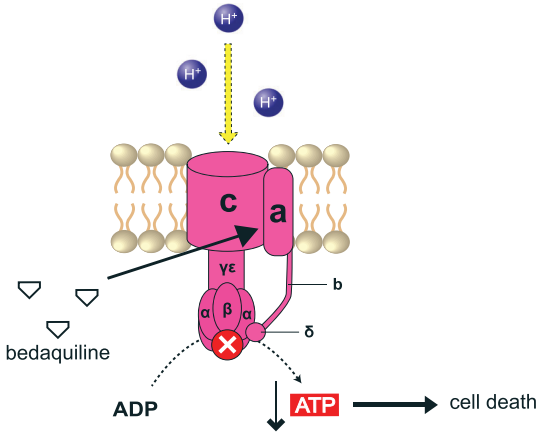

Figure 2

Mechanism of action of bedaquiline. Bedaquiline binds to the transmembrane F_0 region of ATP synthase (between the a and c subunit). This blocks the proton flow through the enzyme and the conformational changes of the enzyme. As a result, the ATP production at the $\alpha_3\beta_3$ hexamer is inhibited. This results in cell death in both replicating and non-replicating mycobacteria

Adverse effects

Common side effects (≥10%) of bedaquiline are headache, dizziness, nausea, vomiting and arthralgia (joint pain). Prolongation of the QT interval has been reported in some patients receiving bedaquiline [1–6].

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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